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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,764	09/27/2000	Joseph R. Piscegna	M-8978 US	7433

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EXAMINER

KAM, CHIH MIN

ART UNIT PAPER NUMBER

1656

DATE MAILED: 10/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/671,764	Applicant(s) PISEGNA ET AL.	
	Examiner Chih-Min Kam	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-10, 20-29, 31 and 32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-10, 20-29 and 31-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

1. Claims 1-4, 6-10, 20-29 and 31-32 are pending.

Applicants' amendment filed August 7, 2006 is acknowledged, and applicants' response has been fully considered. Claims 1 and 20 have been amended. Therefore, claims 1-4, 6-10, 20-29 and 31-32 are examined.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Previous rejection of claims 1-4, 6-10, 20-29 and 31-32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is maintained.

The specification is not enabling for a method of increasing the efficacy of a gastric H^+/K^+ -ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin or a gastrin in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing a pentagastrin or a gastrin because the specification only discloses cursory conclusions without data supporting the findings, which state that the present invention provides a method of treating pathological conditions characterized by excess gastric acid secretion, in particular the method of administering a gastrin, a pentagastrin or an

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analog thereof in conjunction with a PPI, which will result in increased efficacy, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI and a container containing pentagastrin (page 2, line 7-page 4, line 2).

However, there are no indicia that the present application enables the full scope of the claim in view of a method of increasing the efficacy of a PPI in a human in need of PPI treatment and a kit for the treatment of pathology of excess gastric acid secretion as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses variants regarding a gastrin or a pentagastrin being used with a PPI in a combination therapy to treat a human in need thereof, and the effect of gastrin or pentagastrin on the efficacy of PPI in the treatment, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for administering pantoprazole to healthy humans having pentagastrin (1 µg/kg/hr) -induced gastric acid secretion and monitoring the effect of pantoprazole in the

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inhibition of pentagastrin-induced gastric acid secretion (Example 1). The specification has not demonstrated administration of a pentagastrin or a gastrin can increase the efficacy of PPI in the treatment of a patient in need of such treatment.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Simon *et al.*, Aliment. Pharmacol. Therap. 4, 239-245 (1990)) indicates the effect of a PPI, BY1023/SK&F 96022 on the pentagastrin (0.6 µg/h/kg)-stimulated acid secretion in healthy male volunteers. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, or a gastrin in conjunction with a PPI, and the effect of the gastrin or pentagastrin peptide in increasing the efficacy of the PPI in a human in need of a PPI treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of increasing the efficacy of a PPI in a human in need of a PPI by administering an effective amount of a gastrin or pentagastrin in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and a gastrin peptide. However, the in vivo effects of using an effective amount (e.g., 0.1-10 mg/kg/hr) of a gastrin or a pentagastrin to increase the efficacy of a PPI in a human in need of PPI treatment are not adequately described or demonstrated in the specification. While the specification describes pentagastrin is an agent that is typically to increase acid secretion (page 2, lines 9-10), and PPIs are potent inhibitors of gastric acid secretion by inhibiting H⁺/K⁺-ATPase (page 2, lines 1-5); and Example 1 indicates pentagastrin (1 µg/kg/hr, not in the range of 0.1-10 mg/kg/hr) is administered continuously to induce hypersecretion in healthy subjects, and single

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doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner, the specification has not demonstrated administration of an effective amount of pentagastrin such as 0.1-10 mg/kg/hr can increase the efficacy of PPI in inhibiting gastric acid secretion in a human in need of PPI treatment as compared to the efficacy of using PPI alone, especially considering infusion of pentagastrin can stimulate gastric acid secretion (see Example 1 of the specification and Simon *et al.* 1990), which has opposite effect to the PPI. Since the specification indicates gastrin and the PPI can be administered by any route, preferably, the gastrin is administered by injection and PPI is administered orally by injection, and fusion of pentagastrin at 1 µg/h/kg can induce gastric acid secretion (Example 1), the effect of administering pentagastrin (e.g., at 0.1 to 10 mg/kg/h) with PPI in the treatment of excess gastric acid secretion in a human in need of PPI treatment is unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of increasing the efficacy of a PPI in mammal by administering a gastrin or a pentagastrin in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and a gastrin or pentagastrin. The specification indicates the pentagastrin can be administered before, simultaneously with or after the PPI administration with the general dosages (0.1-10 mg/kg/hr) for pentagastrin, gastrin, or analogs thereof (page 2), and Example 1 demonstrates single doses of *i.v.* pantoprazole ranging 20-120 mg suppressed gastric acid secretion in a dose-dependent manner in healthy subjects under continuous pentagastrin (1 µg/kg/hr) -induced hypersecretion. However, the specification has not demonstrated an effective amount (0.1-10 mg/kg/hr) of a gastrin or a pentagastrin

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increases the efficacy of a PPI in a human in need of PPI treatment as compared to the efficacy of PPI using alone. Moreover, there are no working examples indicating the effect of a gastrin, or a pentagastrin in increasing the efficacy of various PPIs in a human in need of PPI treatment. Because pentagastrin has also an effect of inducing gastric acid secretion other than increasing efficacy of PPI, it is unpredictable about the effect of pentagastrin on gastric acid secretion in the combination therapy. Since the specification does not provide sufficient teachings on the use of a gastrin or a pentagastrin in conjunction with a PPI, and the in vivo effects of these peptides in increasing efficacy of PPI and inducing gastric acid secretion in a human in need of PPI treatment, it is necessary to carry out undue experimentation to assess the effects of a gastrin or a pentagastrin in the combination therapy.

(6). Nature of the Invention

The scope of the claims encompasses a method of increasing the efficacy of a PPI in a human in need of a PPI by administering a gastrin or a pentagastrin in conjunction with the PPI, but the specification has not provide sufficient teachings, nor has demonstrated the use and effect an effective amount of the peptide in conjunction with a PPI in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods in associated with variants, the effect of the variant is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to assess the effects of administering a gastrin or a pentagastrin in the method of increasing efficacy of various PPIs in a human in need of PPI treatment.

Response to Arguments

Applicant indicates that the claims simply require administration of a PPI in conjunction with a pentagastrin or a gastrin. In the instant case, proton pump inhibitors (PPIs) are well known to those of skill in the art, are routinely administered to humans. Similarly, both gastrin and pentagastrin have been administered to various animals and humans, e.g. as a model system (see, e.g., Example 1) and tolerances of humans for gastrin and pentagastrin are well known to those of skill in the art. Thus, the art recognizes standard modes of administration of both PPIs and gastrin/pentagastrin, and routine optimization of dosages is readily accomplished by one of skill in the art without undue experimentation. Furthermore, the specification has provided objective evidence that pentagastrin increases the efficacy of a typical PPI as stated in the previous response, and the reference by Bardan et al. (2004) Supplement to Gastroenterology, 12(4): Suppl. 2, Abstract M1439, which indicates that prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitory effect of omeprazole (a PPI) on acid secretion. This effect is mediated by a local effect of PG. Co-administration of PG and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole. Thus, this published scientific literature thus clearly teaches prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitory effect of omeprazole (a PPI) on acid secretion, while the pending claims are drawn to a method of increasing the efficacy of a gastric H⁺/K⁺-ATPase pump inhibitor (PPI) in a human in need of a PPI by administering a PPI in conjunction with pentagastrin or gastrin. It is well accepted law that a post-filing reference can be used to support the operability of a claimed method. Similarly the rat model discussed in Bardan et al. is a standard model for the gastric secretion system and is believed to be predictive for efficacy in humans. The Examiner

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has failed to provide any objective evidence to refute Barda et al. Specifically the Examiner has offered no objective basis to establish why the pentagastrin/omeprazole combination is not predictive for the combination of gastrin or pentagastrin and any other PPI. Similarly the Examiner has offered no objective basis to establish why the rat model is not a good model for behavior of these agents in humans. Thus, the rejection under 35 U.S.C. § 112, first paragraph/35 U.S.C. § 101(a) should be withdrawn (pages 5-9 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because of the following reasons. While the specification demonstrates continuous infusion of pentagastrin at 1 µg/kg/hr induces hypersecretion in healthy subjects, and single doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner, the specification has not demonstrated the synergistic effect of the combination therapy using gastrin/pentagastrin and PPI in the treatment of human in need of PPI treatment. The specification indicates infusion of pentagastrin can induce gastric acid secretion, however, it does not provide sufficient teachings on the use and effect of gastrin/pentagastrin in increasing efficacy of PPI in the combination therapy. The Examiner does not dispute that the *in vitro* data and animal model are sufficient to establish the therapeutic utility for a compound when the correlation exists between the *in vitro* data and *in vivo* test, however, the claimed method of the instant application is directed to a method of increasing efficacy of a PPI in a human subject in need of PPI treatment, which is not directly correlated to the co-administration of oral pentagastrin and omeprazole in the rat model as indicated in Bardan et al., because the specification indicates gastrin/pentagastrin and the PPI can be administered by any route, preferably, the gastrin is administered by injection (e.g., subcutaneous injection), and PPI is

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administered orally by injection (e.g., intravenous injection), particularly, the preferred pentagastrin/gastrin dosage range from 0.1 to 10 mg/kg/hr (page 2, lines 26-31), which refers to infusion method, while Bardan et al. (2004) teach co-administration of oral pentagastrin enhances the efficacy of PPI (i.e., omeprazole) in rat model (i.e., increasing gastric pH), thus the local effect of pentagastrin on omeprazole in the combination therapy as taught by Bardan *et al.* cannot be used as evidence to support the claimed method, which does not require oral administration of gastrin/pentagastrin. Furthermore, Bardan *et al.* indicate co-administration of oral pentagastrin and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole, which also suggests undue experimentation is needed to assess the effect of pentagastrin in potentiating omeprazole in the clinical treatment. Moreover, Bardan et al. (2004) is a post filing reference, which may be used to support the argument regarding enablement issue, but the content of the reference cannot be used as the omitted teachings for the specification at the time of filing of the instant application. Thus, the enablement rejection is maintained. Please call Examiner to set up a telephone interview, if applicant wants to discuss the issue.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 31 is indefinite because the claim has the same scope as claim 24, since claim 31 recites "said one or more agents is pentagastrin" and depends from claim 24, which recites "said PPI is dehydrated", while claim 24, which recites "said PPI is dehydrated", is dependent from claim 21, which recites the limitation "said one or more agents is pentagastrin".

Response to Arguments

Applicants indicate claim 24 is directed to a kit comprising "a container containing a proton pump inhibitor (PPI); and a container containing one or more agents selected from the group consisting of a pentagastrin, and a gastrin" where the "PPI is dehydrated." Claim 31 is directed to a kit as recited in claim 24 where "said one or more agents is pentagastrin". This language further limits the earlier recitation of "one or more agents selected from the group consisting of a pentagastrin, and a gastrin". Claim 31 thus has different scope than claim 24 and the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn (page 9 of the response).

Applicants' response has been fully considered, however, the argument is not found persuasive because claim 24 is also dependent from claim 21, thus claim 24 is directed to a kit, where the "PPI is dehydrated" and where "said one or more agents is pentagastrin", which has the same scope as claim 31. Therefore, the rejection is maintained.

Conclusion

4. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 24, 2006